FDA Briefing Document

Cardiovascular and Renal Drugs Advisory Committee Meeting

December 16, 2020

Spironolactone for Heart Failure with Preserved Ejection Fraction (HFpEF)

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1. Introduction

This is a review of the NHLBI-sponsored TOPCAT[1] trial of spironolactone in adult patients with heart failure with preserved ejection fraction (HFpEF). (1) (2) The intent of the review was to analyze the available publications, study documents, and data from the trial to determine whether this information supports a labeled indication for spironolactone in the treatment of adults with HFpEF.

There is no NDA, NDA supplement, or applicant requesting the labeling change described above. This review and any regulatory activity that may occur in response to its recommendations are self-directed efforts by FDA staff to respond to an important, unmet medical need for treatments to improve clinical outcomes in patients with HFpEF, a serious and sometimes fatal condition for which there are presently no treatments approved to affect the course of the disease.

2. Draft Topics for Discussion

The Committee will be asked to opine on spironolactone for heart failure with preserved ejection fraction.

Spironolactone has a claim for the treatment of heart failure with reduced ejection fraction, so this would be a new indication. In this case, there is no applicant—although the Agency tried to solicit interest—so the review was undertaken on the initiative of the Division. If a favorable decision is reached, the Agency will make clear the conditions under which the claim can be obtained.

Section 505(d) of the 1962 Drug Amendments included a provision requiring manufacturers of drug products to establish a drug's effectiveness by *substantial evidence*, defined as *evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling….* We would like you to provide your insights as such experts. As always, your rationale is more important to us than is your vote.

The study supporting this claim is TOPCAT, but this study did not meet its prespecified success criterion for the primary endpoint. Approval under this circumstance is unusual but not unprecedented. Some examples are:

- Enalapril was approved for use in asymptomatic left ventricular dysfunction on the basis of SOLVD-Prevention.
- Digoxin for heart failure was approved on the basis of the DIG study
- Carvedilol was approved for reduced ejection fraction following myocardial infarction on the basis of the CAPRICORN study.
- Bivalirudin was approved for use after PCI on the basis of the post-hoc pooling of the BAT studies.

[1] TOPCAT is the acronym for the "Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone AnTagonist" trial.

Like the current case, all of the above involved new indications for approved drugs for relatively common cardiovascular diseases, but the extenuating circumstances were different. In TOPCAT, there are reasons to question the applicability of results obtained in some parts of the world. Although not detailed in the review, the review team devoted a considerable effort to look for criteria for the inclusion or exclusion of sites based on baseline data; none seem as compelling as "region". While exclusion of a region is exceptional, exclusion of a site is not rare, when there are reasons to question the validity of the data.

1. Please comment on the various pre-specified and post-hoc analyses. Which ones contribute to your assessment of the strength of evidence supporting a claim? Which ones do not?
2. Does TOPCAT provide sufficient evidence to support ANY claim?
3. If a claim for spironolactone were not granted on the basis of available information, what would be necessary to augment the support for approval?
4. If spironolactone warranted a claim, how would you describe the patients in whom such benefit applies?

3. Summary of Conclusions Regarding Benefits and Risks

TOPCAT was an NIH-sponsored, placebo-controlled trial that was conducted at sites in North America, South America (collectively, "the Americas") and Eastern Europe, and was completed in 2013. It compared a titrated regimen of oral spironolactone to placebo in patients with HFpEF. The trial failed to reject the null hypothesis for its primary outcome of time to the composite of cardiovascular (CV) death, hospitalization for HF (HHF), or aborted cardiac arrest. Overall, in the 3445 randomized subjects, the rate of the primary endpoint was 5.9 vs. 6.6 events per 100 person-years in the spironolactone and placebo arms, respectively [hazard ratio (HR)=0.89; 95% confidence interval (CI), 0.77, 1.04; log-rank p=0.14]. Nearly all the primary endpoint events that occurred were either deaths or HHF (**Table 7**).

There were notable differences between the results in subgroups based on region (the Americas, with 51% of study subjects vs. Eastern Europe, with 49% of subjects). Results for the primary outcome slightly favored placebo over spironolactone in Eastern Europe, but in the Americas, there was a nominal 18% reduction in the rate of the primary outcome with spironolactone, compared to placebo. In the Americas, the results favored spironolactone over placebo for both death and HHF, including both first HHF and cumulative HHF (**Table 1**).

Table 1. Regional Results for the Primary Outcome, its Components, and Cumulative Heart Failure Hospitalization

Region / Outcome	SPIRONOLACTONE n (%)	%/year	PLACEBO n (%)	%/year	HR (95% CI) or *IRR (95% CI)
The Americas	**N=886**		**N=881**		
Primary Outcome	**242 (27.3)**	**10.4**	**280 (31.8)**	**12.6**	**0.82 (0.69–0.98) p=0.026#**
CV Death	96 (10.8)	3.6	127 (14.4)	4.9	0.74 (0.57–0.97)
Aborted Cardiac Arrest	2 (0.2)	0.08	4 (0.5)	0.16	-
HHF	184 (20.8)	7.9	216 (24.5)	9.7	0.82 (0.69–0.99)
Cumulative HHF	**361**	**13.7**	**438**	**17.0**	**0.75 (0.58-0.96)**
Eastern Europe	**N=836**		**N=842**		
Primary Outcome	**78 (9.3)**	**2.5**	**71 (8.4)**	**2.3**	**1.10 (0.79-1.51)**
CV Death	64 (7.7)	2.0	49 (5.8)	1.6	1.31 (0.91-1.90)
Aborted Cardiac Arrest	1 (0.1)	0.03	1 (0.1)	0.03	-
HHF	22 (2.6)	0.72	29 (3.4)	0.95	0.76 (0.44-1.32)
Cumulative HHF	**33**	**1.1**	**37**	**1.2**	**0.83 (0.42-1.62)**

HHF= Hospitalization for heart failure; IRR=incidence rate ratio
Ns and rates for cumulative HHF are total numbers of events, not of patients with events.
* Statistical methods are reported to be the same as for the overall analysis, meaning that the *p*-value for the primary endpoint was calculated using a log-rank test and the cumulative HHF analyzed using a negative binomial analysis.
#This *p*-value reflects no correction for multiplicity in considering results in two regions.
Source: Pfeffer et al (3). Results were confirmed by Dr. Liu.

In addition to the reports of the CV outcomes, the study team's various publications included information regarding geographic differences in baseline demographic characteristics of the study subjects, assessments related to the pharmacology of spironolactone, and levels of canrenone, a long-lived metabolite of spironolactone.

These publications describe three broad classes of information that undercut the ability of the data from Eastern Europe to predict the true effects of spironolactone in patients in the US with HFpEF.

- Patient characteristics: There are major differences in the demographic and disease-related characteristics of subjects in the two regions at baseline.

Compared to subjects from the Americas, subjects from Eastern Europe were younger and more likely to have had a history of coronary disease or to be treated with aspirin than those in the Americas. In addition, patients from Eastern Europe were far less likely to have qualified for the study on the basis of elevated natriuretic peptide (NP) levels, which were a predictor of outcome events (**Table 8**).

- Event rates: For the primary endpoint and cumulative HHFs, the event rates in the placebo groups in the two regions were strikingly different. For the primary endpoint, the rates were 2.3 vs. 12.6 per 100 person-years in Eastern Europe vs. the Americas, respectively. The rates of total (first and recurrent) HHF in placebo group patients were 1.2% and 17% in Eastern Europe and the Americas, respectively. Thus, comparing event rates in the placebo groups in Eastern Europe and in the Americas, the rate of the primary endpoint was 5.4-fold higher in the Americas; the rate of total HHF was 14-fold higher. Also, the rates of these events in Eastern Europe were much less than the placebo arm rates in earlier studies of drugs for HFpEF, while the rates in the Americas were in-line with the earlier studies (see **Table 13** and associated text).

- Treatment compliance: Subjects in Eastern Europe who were randomized to receive spironolactone were less likely to have had signs or symptoms related to the common pharmacodynamic effects of spironolactone, i.e., reductions in blood pressure, elevations of serum potassium and/or creatinine, and gynecomastia, suggesting that compliance with study medication was poorer in Eastern Europe than in the Americas.

  Compared to subjects from the Americas, spironolactone arm subjects from Eastern Europe had much lower rates of typical spironolactone PD effects (decreased systolic blood pressure, increased serum potassium, and increased serum creatinine, see **Table 15** and **Figure 5).** They also had lower rates of discontinuation from the study because of breast tenderness and/or enlargement (i.e., gynecomastia), which affects about 9% of men taking spironolactone (**Table 5**).

  Canrenone is a long-lived metabolite of spironolactone that should be present in the serum of patients several days after their last dose of spironolactone. Spironolactone arm patients in Eastern Europe who claimed to be taking their study drug were 10-fold more likely to have undetectable levels of canrenone in their serum than those in the Americas (**Table 15**). These data suggest that the patients in the Eastern Europe had a higher rate of failure to take their study drug than subjects in the Americas.

These observations support the view that the study data from the Americas are much more likely to be predictive of the true effects of spironolactone on outcomes of US patients with HFpEF than the data from the TOPCAT study as a whole.

There are, however, good reasons to be skeptical about accepting the Americas results of TOPCAT.

- While it is not uncommon to exclude the results of a problematic study site, we know of no precedent for exclusions of a whole region that constitutes almost half of the study population. The best estimate of the effect of a study intervention is usually the prespecified

overall result, which, at *p*=0.14, is not close to rejection of the null hypothesis. Further testing in subgroups inflates type I error.

- The test for interaction by region is not close to statistically significant at *p*=0.12, which means we do not have enough evidence to conclude that two regions are so different such that overall results should not be considered.
- The nominal *p*-value in the Americas was 0.026—with no correction for multiplicity. Subgroup analyses do not carry the same level of evidence as a pre-specified hypothesis that the study was designed to test.
- While the interaction by region was not statistically significant, the interaction by enrollment stratum was significant, at *p*=0.01, with benefit shown in patients, mostly in the Americas, enrolled with elevated B-type natriuretic peptide (BNP). However, the BNP stratum constitutes less than 30% of the total population. Patients qualified by a previous HHF in both regions seemed to show no treatment effect in both regions. This is contradictory to the explanation that different populations between two regions led to different outcome.

If one were to conclude that the Americas results were an appropriate basis for a regulatory decision, approval based on a single study is supported by the reduction in death and HF hospitalization, either subjects with any HF hospitalization (part of the primary composite) or cumulative events. This would be consistent with advice in FDA's 2019 draft guidance, "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products."[2]

The safety data from TOPCAT show no new safety signals for spironolactone, a drug that has been on the market in the US since 1962 and is indicated to increase survival and reduce the need for heart failure hospitalization in patients with heart failure and reduced ejection fraction.

4. Background

HFpEF

About half of adults with clinically recognized HF have a normal or near-normal left-ventricular ejection fraction (LVEF). These patients have increased passive ventricular stiffness and reduced ventricular filling, without dilatation of the LV, and typically have characteristic echocardiographic findings during diastole related to these abnormalities. Abnormal diastolic function in these patients leads to increased left atrial and pulmonary venous pressures, with ensuing symptoms of left-sided HF. Hence, HFpEF is sometimes termed "diastolic" heart failure. There may be associated systolic dysfunction, as well as diminished vasodilator reserve. There is often impaired renal handling of salt and water because of increased neurohormonal activation and chronic kidney injury. Although blood levels of the natriuretic peptides (NPs) NT-proBNP and BNP may be elevated in patients with HFpEF, as they are in those with HF with reduced ejection fraction (HFrEF), those with HFpEF tend to have somewhat lower levels of NPs than those with HFrEF. Some outpatients with invasively confirmed HFpEF have normal levels of NPs (4). Thus, the accurate diagnosis of HFpEF may be more complicated than that of HFrEF.

[2] https://www.fda.gov/media/133660/download, accessed 11/13/2020

Patients with HFpEF experience a clinical path and outcomes like those with HFrEF. However, compared to those with HFrEF, patients with HFpEF tend to be older and are more likely to be women. Comorbidities that have been linked to the development of HFpEF are hypertension, obesity and the metabolic syndrome. Given these driving factors and the aging of the population, it is not surprising that the prevalence of HFpEF is increasing at a rate of about 10% per decade. (1),(5)

Because renin-angiotensin system (RAS) inhibitors have been effective in reducing mortality and HHF in patients with HFrEF, there has been interest in studying these agents in patients with HFpEF. However a trial of the angiotensin converting enzyme inhibitor (ACEI) perindopril failed to meet its primary outcome.(6) Also, trials of two angiotensin II receptor blockers (ARBs) in patients with HFpEF were negative.(7),(8) A meta-analysis of controlled trials of beta-blockers in patients with HFpEF failed to find benefits over placebo for any CV outcome.(9) To date, no drug has US labelling that claims improvements in CV outcomes in patients with HFpEF. Effective treatments are clearly needed.

Spironolactone

Spironolactone is a mineralocorticoid receptor antagonist (MRA). The prototypical mineralocorticoid is the adrenal hormone aldosterone. MR agonism in the distal renal tubules and collecting ducts leads to fluid and sodium retention. MR agonism also promotes sodium and water absorption in the colon. These effects expand extracellular fluid volume, leading to increased blood pressure, and produce renal potassium wasting, which is reflected in reduced levels of serum potassium. Spironolactone, which was the first potassium-sparing diuretic, counters these effects, and typically results in elevations of serum potassium and reductions in blood pressure. It also may result in decreased renal function in patients with HF, which is manifested by increases in serum creatinine. It also produces gynecomastia, which was reported at rate of 9% among men in the spironolactone arm of the RALES study (see below for a discussion of this study). Labeling indicates that gynecomastia is “usually reversible.” Additional, more subtle effects of spironolactone that might be relevant to its long-tern use to treat HFpEF are described **below**.

Spironolactone was first approved in the US in 1960 as Aldactone® (GD Searle). A combination tablet with hydrochlorothiazide (Aldactazide®) was also approved then. Spironolactone is available as oral tablets in strengths of 25 mg, 50 mg and 100 mg.

The half-life of spironolactone in humans is ~1.4 hours. It is rapidly metabolized to canrenone, which is also an MRA, and which has a half-life of ~16 hours. Other metabolites also have modest activity as MRAs. Spironolactone is usually dosed once daily (OD), but patients with heart failure and moderate renal dysfunction may be started on 25 mg every other day (QOD). QOD dosing with the 25 mg tablet is also recommended for those who develop hyperkalemia with 25 mg OD.

In the 1960s, indications for Aldactone were the treatment of edema caused by cirrhosis, nephrotic syndrome, heart failure, as well as idiopathic edema; essential hypertension, and cirrhotic ascites. Aldactazide had the same indications. More recently, an indication for treatment of primary hyperaldosteronism was added to labeling of spironolactone monotherapy, but not the combination product.

In 2006, an indication for treatment of NYHA Class III–IV heart failure with reduced ejection fraction to increase survival, manage edema, and reduce the need for hospitalization for heart failure was added to the labeling of spironolactone monotherapy, but not the combination product. This labeling change was based on the results of the RALES study, which was funded by Searle.(9) The efficacy results of RALES are described in spironolactone labeling as follows:

> "The primary endpoint for RALES was time to all-cause mortality. RALES was terminated early because of significant mortality benefit demonstrated during a planned interim analysis. Compared to placebo, spironolactone reduced the risk of death by 30% ($p<0.001$; 95% confidence interval 18% to 40%). Spironolactone also reduced the risk of hospitalization for cardiac causes (defined as worsening heart failure, angina, ventricular arrhythmias, or myocardial infarction) by 30% ($p<0.001$; 95% confidence interval 18% to 41%)."

Also, the RALES primary publication indicates that there was a 31% reduction in the rate of CV mortality with spironolactone.(10)

Aldactone and Aldactazide are still marketed by Searle, which is now a subsidiary of Pfizer. There are also multiple generic versions of spironolactone tablets and spironolactone + hydrochlorothiazide (HCTZ) tablets. The generics have indications similar to the respective branded products. Carospir®, a suspension of spironolactone (25 mg/5 mL), is marketed by CMP Pharma, Inc, with indications for hypertension, HFrEF and edema caused by cirrhosis, under (NDA 209478), approved in 2017. There are no generic spironolactone suspensions.

No formulation of spironolactone marketed in the US matches the dose used in TOPCAT.

TOPCAT Rationale, Objectives and Design

The TOPCAT design paper by Desai et. al.(1) describes the rationale for use of spironolactone to treat HFpEF as follows:

> "Experimental evidence indicates that aldosterone blockade reduces collagen deposition (fibrosis) within the myocardium and the vasculature, improves vascular compliance and endothelial function, decreases inflammation and oxidative stress, increases myocardial perfusion and capillary density, and limits inducibility of atrial fibrillation. Accordingly, in clinical studies of elderly patients with hypertensive heart disease and diastolic dysfunction, spironolactone treatment appears to improve myocardial relaxation, reduce left ventricular hypertrophy and central aortic stiffening, and improve functional capacity. Prospective, randomized clinical trials of aldosterone antagonists have demonstrated efficacy in reducing mortality among patients with severe symptomatic HF and reduced ejection fraction (EF) as well as those with myocardial infarction complicated by HF or left ventricular dysfunction. Most recently, a randomized trial of eplerenone [another MRA] in stable patients with less severe (New York Heart Association [NYHA] II) HF was stopped early for evidence of overwhelming efficacy, confirming the benefits of aldosterone inhibition across the full spectrum of HF with reduced LVEF….
>
> "Both these mechanistic data and the demonstrated morbidity and mortality benefits of spironolactone in patients with HF and reduced LVEF provide the rationale for a randomized clinical trial of mineralocorticoid inhibition in HF-PEF. The TOPCAT trial (clinicaltrials.gov, NCT00094302) is funded by the National Heart, Lung, and Blood Institute (NHLBI) as a contract to evaluate the long-

> term safety and effectiveness of spironolactone in patients with symptomatic HF-PEF." [citations omitted]

The primary objective of the trial was to evaluate the efficacy of spironolactone relative to placebo on the cumulative incidence of the composite primary outcome of CV death, HF hospitalization, or aborted cardiac arrest in patients with symptomatic HF and LVEF ≥45%.

Design Features

TOPCAT was a double-blind, placebo-controlled RCT conducted at 233 sites in 6 countries in two regions. The countries with study sites were the US, Canada, Brazil and Argentina (collectively, "the Americas") and Russia and Georgia ("Eastern Europe"). The trial was sponsored by the National Heart, Lung and Blood Institute (NHLBI). The trial was run under research IND 71883, held by Dr. Robin Boineau, MD, of NHLBI.

Patients:

Key inclusion and exclusion criteria are shown in **Table 2**.

Table. 2 Key Eligibility Criteria for TOPCAT

Inclusion Criteria	Exclusion Criteria
1. Age ≥50 y 2. HF signs and symptoms (see text below table) 3. LVEF ≥45% confirmed within 6 months before randomization 4. Systolic blood pressure <140 mm Hg **or** ≤160 mm Hg and on treatment with ≥3 antihypertensive medications 5. Serum potassium <5.0 mmol/L 6. (a) Hospitalization for which management of HF was a major component within 1 year before randomization **or** (b) Elevated natriuretic peptides (NPs) within 60 days before randomization (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL). (There were no alternative NP criteria for patients with atrial fibrillation.)	1. Severe systemic illness with life expectancy <3 years from randomization 2. Severe chronic obstructive pulmonary disease (e.g., requiring home oxygen or chronic oral steroid therapy) 3. Known restrictive/infiltrative cardiomyopathy, hypertrophic cardiomyopathy, or constrictive pericarditis 4. Hemodynamically significant valvular heart disease (e.g., valvular disease anticipated to require surgical correction during the trial) 5. Atrial fibrillation with a resting heart rate >90/min 6. Systolic blood pressure >160 mm Hg 7. History of hyperkalemia (≥5.5 mmol/L within the last 6 months or ≥5.0 mmol/L in the last 2 weeks) 8. Severe renal dysfunction, defined as eGFR <30 mL/min per 1.73 m^2 or serum creatinine ≥2.5 mg/dL 9. MI, coronary artery bypass graft surgery, or stroke within 90 d before randomization; percutaneous coronary intervention within 30 days before randomization 10. Use of aldosterone antagonist or potassium sparing diuretic within 14 days before randomization

The study protocol included explicit guidance regarding the requirement for signs and symptoms of HF. Each patient was required to have at least one of 3 named symptoms at screening (paroxysmal nocturnal dyspnea, orthopnea, or dyspnea on mild or moderate exertion) and also was required to have at least one of 4 named signs of HF (any rales post cough, jugular venous pressure ≥ 10 cm H_2O, lower extremity edema, or chest X-ray demonstrating pleural effusion, pulmonary congestion, or cardiomegaly) either at screening or in the previous 12 months.

Study Treatments

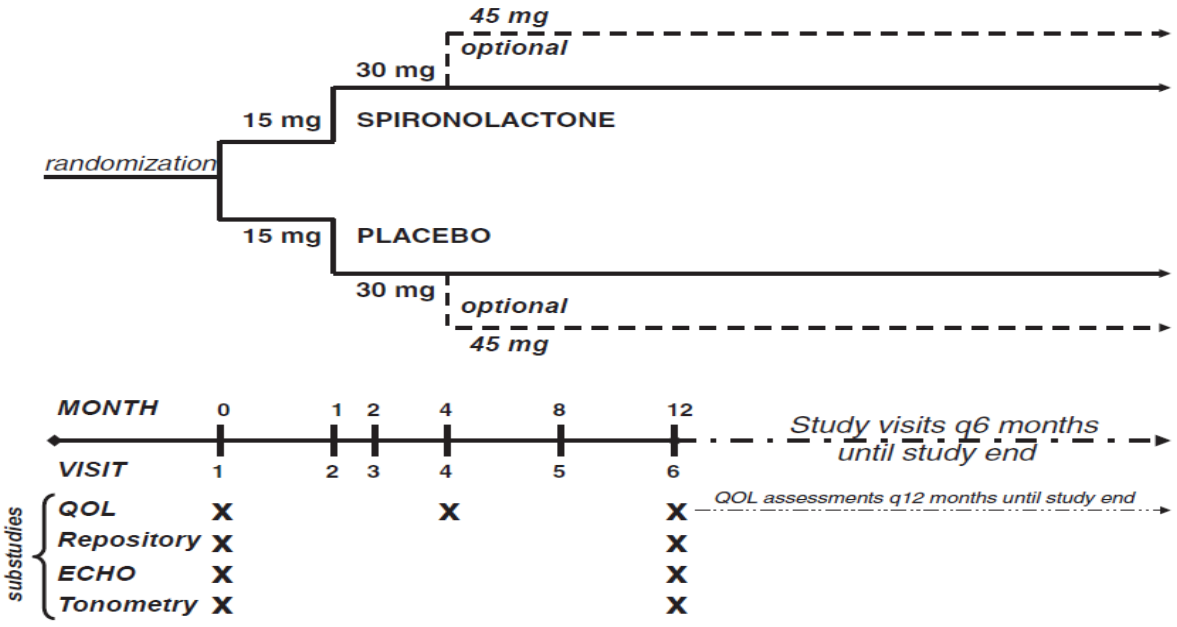
A unique formulation of spironolactone was used in this study: a 15-mg tablet, manufactured by URL Mutual Pharmaceuticals of Philadelphia. There was a matching placebo. The novel tablet was used "…because of the desire to initiate spironolactone at a lower dose than the smallest commercially available 25-mg tablet."(1)

Dosing in TOPCAT was started at one 15-mg tablet daily. If this dose was tolerated, the dose was increased to 30 mg daily at the Week 4 visit. For those tolerating this dose and with acceptable values of serum creatinine and potassium, at the Month 4 visit the dose could be increased at the investigator's discretion to 45 mg daily to control HF symptoms. Of note, the average dose of spironolactone in the successful RALES trial in patients with HFrEF was 26 mg daily.

Study Plan and Assessments

The TOPCAT study plan is shown in **Figure 1**.

Figure 1. TOPCAT Study Plan



The TOPCAT schema and study visit schedule. QOL indicates quality of life; ECHO, echocardiography.

The schedule of visits and assessments is shown in **Table 3**. Urine and blood samples collected as a "repository specimen" at selected sites were later analyzed for canrenone levels, an important indicator of compliance for patients in the spironolactone arm. Safety labs, including serum electrolytes, blood urea nitrogen (BUN), and creatinine, were collected one week after any change in the dosing regimen, and also at each scheduled study visit during the treatment period.

Endpoints and Sample Size

The primary outcome was a time to event analysis of the composite of CV mortality, aborted cardiac arrest, or hospitalization for the management of HF, analyzed using a two-sided log-rank test at an alpha of 0.05, with no covariates. Subjects were censored at the time of last contact, except for patients undergoing heart transplant prior to the last contact, who were censored at the time of the transplant procedure. The protocol also stated that a Cox model comparison of the treatment arms would be run as a secondary analysis.

Other efficacy outcomes included: the individual components of the primary outcome; all-cause mortality; CV mortality or CV related hospitalization (i.e.., for non-fatal MI or stroke, or for HF); an incidence rate analysis of HF hospitalization to account for recurrent events;[3] and sudden death or aborted cardiac arrest, the rate of new findings such as atrial fibrillation (A Fib), onset of diabetes mellitus, MI, stroke, deterioration of renal function; and sudden death, aborted cardiac arrest, or hospitalization for management of ventricular tachycardia. The issue of alpha allocation was not addressed in the protocol with respect to these endpoints. The protocol also specified the primary endpoint would be evaluated in a long list of subgroups, starting with subgroups based on enrollment stratum (history of HHF in the 12 months prior to study entry vs. elevated NPs). No alpha error was allocated to these subgroup analyses.

Three interim looks at the study data were planned, with an early stopping rule based on a Lan-Demets version of an Obrien-Fleming group sequential plan. The study was not stopped early, and the final alpha was 0.0498.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was administered at baseline and then at Months 4, 12, and yearly after that, and was the primary quality of life (QOL) assessment. The KCCQ estimand of interest was not specified in the protocol. Other QOL instruments included the EuroQOL Health Status Questionnaire (EQ-5D), the McMaster Overall Treatment Evaluation (OTE), and the Patient Health Questionnaire.

Endpoint events were adjudicated at the Brigham and Women's Hospital, Boston, MA. Adjudicated events included death, hospitalization for congestive heart failure, cardiac arrest, myocardial infarction, and stroke. Adjudicators were blinded to study treatment.

When designed in 2005, the trial was intended to enroll 4500 patients and follow them over 3.25 years. The intent was to provide 90% power to detect a 20% reduction in the rate of the primary outcome. However, in 2009, accruing study data suggested that the original estimates of the event rate in the placebo arm seemed too high. Thus, study power was re-estimated using a placebo arm primary endpoint event rate of 17.4% over 3 years, based on placebo arm data for HF death and HF hospitalization in the I-PRESERVE trial (6), a 20% effect size for the primary endpoint comparison, a mean follow-up period of 3.75 years, and a 3% increase in sample size to account for alpha error

[3] The protocol (downloaded from the NEJM website) states that this parameter would be analyzed using a Poisson regression, while the primary publication (Pitt et. al. (2)) indicates that a negative binomial regression was used to account for "correlated events."

spent on interim analyses. The revised study would have 80% power to detect a difference between spironolactone and placebo with 3515 enrolled subjects.(1)

Trial Conduct

There was no plan for routine periodic site monitoring. Instead, the protocol stated,

> "All sites will be visited at least once during the trial by representatives from the CTCC, Regional leader teams, and/or the sponsor. Additional visits will generally be reserved for sites with problems (audits for cause). The monitoring visit consists of reviewing and evaluating three separate components: conformance to IRB/EC and consent form requirements, compliance to trial protocol, and source document data verification. Any site found to be Unacceptable or Acceptable/Needs Follow-up on any monitoring visit is required to submit a written response and/or corrective action plan to the CTCC within 21 days of the receipt of the final monitor findings. Sites that fail to meet the standards for acceptable performance will undergo follow-up action, which will be determined by the severity of the discrepancies and may include repeat on-site monitoring, probation, or suspension."

Table 3. Schedule of Visits and Assessments

	Record Screening	Baseline Screening	Randomization and Drug Distribution	1 Week	4 Weeks	5 Weeks	8 Weeks	4 Months	8 Months	12 Months	18 Months	24, 36, 48 Months	30, 42, 54 Months
Medical History	X	X											
Current Medications	X	X			X		X	X	X	X	X	X	X
Echocardiogram*	X												
Physical Exam, Wt., Vital Signs		X			X		X	X	X	X	X	X	X
Assessment of Study Drug Compliance				X	X	X	X	X	X	X	X	X	X
Blood Studies**		X		X***	X	X	X	X	X	X	X	X	X
ECG		X											
Adverse Event Monitoring				X	X	X	X	X	X	X	X	X	X
Urine Microalbuminuria		X								X		X	
QOL****		X						X		X		X	
Repository Specimens													
Urine Specimen		X								X			
Blood Specimen		X								X			
DNA Specimen		X											

* Ejection fraction obtained within 6 months prior to randomization and after any MI or other event that would affect ejection fraction.
** Blood Studies (local lab):
- Baseline blood studies include: CBC, electrolytes, BUN, creatinine, blood glucose, and LFTs.
- Follow-up safety blood studies include: electrolytes, BUN and creatinine.

*** Safety labs will be collected at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped).
**** OTE instrument will only be administered at the 4 and 12 month visits; KCCQ and EQ-5D instruments will only be administered at Baseline, 4 and 12 month visits and annually thereafter; Patient Health Questionnaire instrument will only be administered at Baseline and 12 month visits and annually thereafter.

5. Study Results

5.1 Study Subjects

TOPCAT enrolled subjects from August 2006 through January 2012 and followed them to their first semi-annual visit in 2013 (no later than June 30). The study ended as planned with no early termination. A total of 3445 subjects were randomized (1722 to spironolactone, 1723 to placebo). Mean follow-up was 3.3 years. Characteristics of the study subjects, including demography, co-morbid conditions, and baseline medication use, are shown in **Table 4**. The study arms were similar for all listed characteristics. About 71.5% of subjects entered the study on the basis of a prior HF hospitalization; the remainder had elevated baseline NP levels.

Table 4. Subject Characteristics at Baseline (All Randomized Subjects)

Characteristic	Spironolactone (N = 1722)	Placebo (N = 1723)
Median Age — (years)	68.7	68.7
Age ≥75 years — n (%)	495 (28.7)	453 (26.3)
Female sex — n (%)	888 (51.6)	887 (51.5)
White race — n (%)	1525 (88.6)	1537 (89.2)
Median LVEF (%)	56	56
NYHA class — n (%) I	56 (3.3)	53 (3.1)
II	1090 (63.3)	1104 (64.1)
III	568 (33.0)	553 (32.1)
IV	7 (0.4)	8 (0.5)
Missing	1 (<0.1)	5 (0.3)
Eligibility Stratum – n (%) Elevated NPs	490 (28.5)	491 (28.5)
BNP - pg/mL - Median at baseline	*236*	*235*
NT-proBNP- pg/mL- Median at baseline.	*887*	*1017*
HF Hospitalization	1232 (71.5)	1232 (71.5)
Heart Rate – BPM – Median	68	68
Systolic BP - mmHg	130	130
Diastolic BP - mmHg	80	80
BMI – kg/m^2 - Median	31	31
Serum K – mEq/L - Median	4.3	4.3
Serum Cr – mg/dL - Median	1.0	1.1
eGFR – mL/min/1.73 m^2 - Median	65.3	65.5
Hemoglobin – g/dL- Median	13.2	13.3

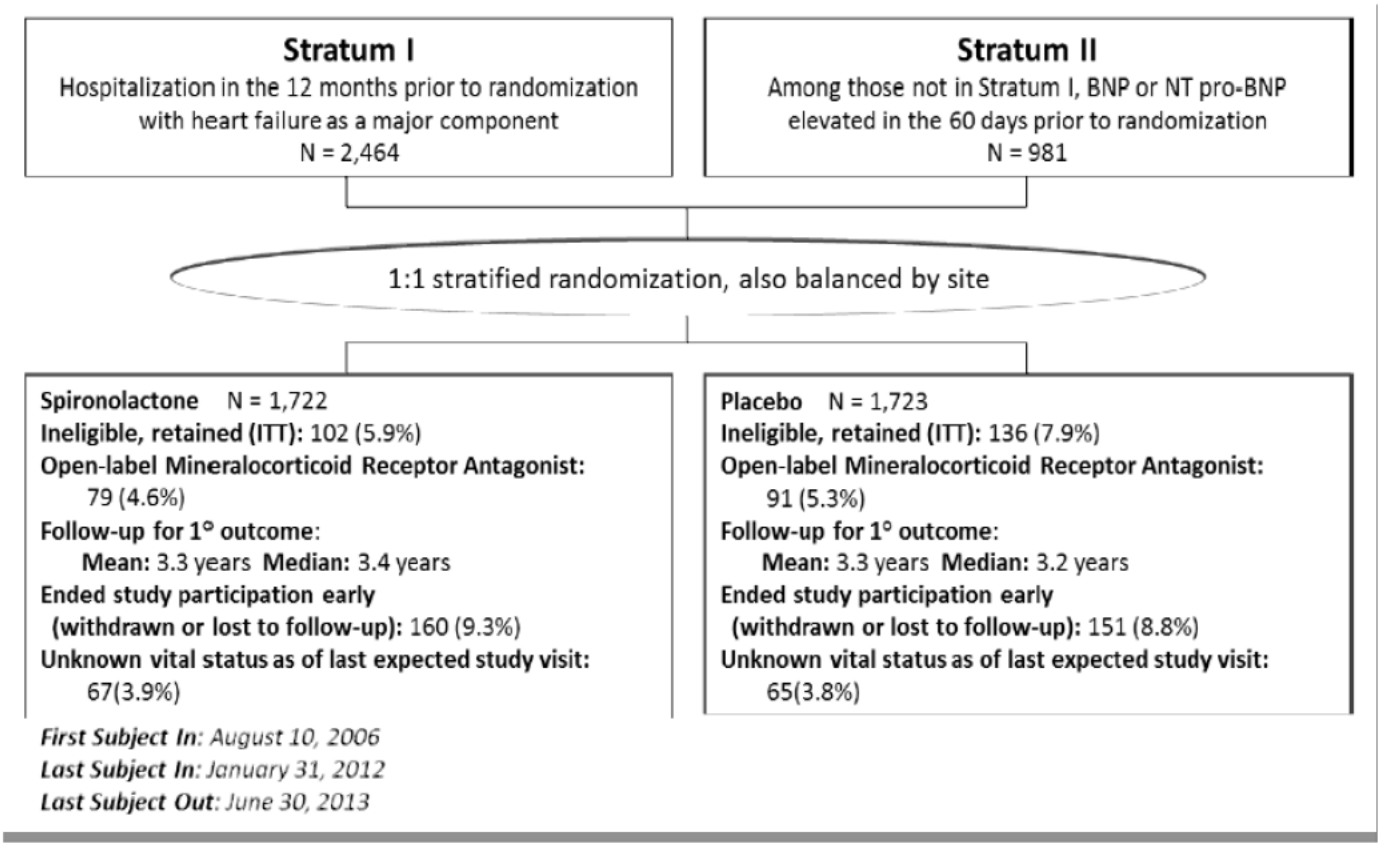
Characteristic	Spironolactone (N = 1722)	Placebo (N = 1723)
Region of enrollment – n (%) Americas	886 (51.5)	881 (51.1)
Eastern Europe	836 (48.5)	842 (48.9)
CO-MORBID ILLNESS **n (%)**		
Coronary artery disease	989 (57.4)	1034 (60.1)
Atrial fibrillation	611 (35.5)	603 (35.1)
Diabetes mellitus	565 (32.8)	553 (32.2)
Insulin-treated	218 (12.7)	209 (12.2)
Chronic kidney disease (eGFR<60 ml/min/1.73m sq.)	672 (39.0)	660 (38.3)
Hypertension	1567 (91.0)	1580 (91.9)
Myocardial infarction	444 (25.8)	449 (26.1)
PCI or CABG	403 (23.4)	410 (23.8)
Dyslipidemia	1011 (58.7)	1062 (61.7)
COPD	209 (12.1)	194 (11.3)
Stroke	128 (7.4)	137 (8.0)
BASELINE MEDICATIONS **n (%)**		
Diuretic	1401 (81.4)	1416 (82.3)
ACEI or ARB	1452 (84.3)	1448 (84.2)
Beta-blocker	1346 (78.2)	1330 (77.3)
Calcium channel blocker	625 (36.3)	669 (38.9)
Aspirin	1122 (65.2)	1128 (65.6)
Statin	910 (52.8)	895 (52.0)
Long acting nitrate	262 (15.2)	252 (14.7)
Warfarin	403 (23.4)	384 (22.3)

ACEI=ACE inhibitor; ARB=angiotensin II receptor blocker
Source: Pitt et. al. (2)

Disposition

Patient disposition data, reproduced from the published CONSORT diagram, are shown in **Figure 2**. Early loss to follow-up was about 9% in each arm. Vital status was unknown at the last study visit in about 4% in each arm.

Figure 2. TOPCAT Consort Diagram (All Subjects, N=3445)



Source: Pitt et. al. (2)

The rates of early discontinuation of study drug in subjects who continued participation in the study were 34% and 31% in the spironolactone and placebo arms, respectively (**Table 5**). As expected, more patients in the spironolactone arm discontinued for reasons relating to hyperkalemia, decreased renal function, and gynecomastia.

Table 5. Early Permanent Discontinuation of Study Drug in Subjects Who Continued Study Participation

Discontinuation Status	N (%) among all randomized individuals	
	Spironolactone N=1722	Placebo N=1723
Any early permanent discontinuation of study drug	**590 (34.3)**	**541 (31.4)**
Time from study entry to early permanent discontinuation		
< 1 year	292 (17.0)	232 (13.5)
≥ 1 year but < 2 years	140 (8.1)	114 (6.6)
≥ 2 year but < 3 years	69 (4.0)	81 (4.7)
≥ 3 years	89 (5.2)	114 (6.6)
No early permanent discontinuation	**1132 (65.7)**	**1182 (68.6)**
Reasons for permanent discontinuation,		
Persistent hyperkalemia	45 (2.6)	17 (1.0)
Potassium > 5.5 mEq/L on lowest dose of study drug	101 (5.9)	20 (1.2)
Abnormal renal function	67 (3.9)	39 (2.3)
Anaphylactoid reaction or intolerance	6 (0.4)	11 (0.6)
Breast tenderness or enlargement	43 (2.5)	5 (0.3)
Open-label use of aldosterone antagonist or potassium-sparing diuretic	21 (1.2)	51 (3.0)
Other	369 (21.4)	418 (24.3)

Source: Pitt et. al. online supplement (2), Table S3 (b)
Note: Some patients are represented in more than one row regarding reasons for discontinuation

The distribution of daily dose of study drug for subjects at the Month 8 visit is shown in **Table 6**. Note that patients who tolerated study drug well could have been titrated up to 45 mg at Month 4. Most subjects in the spironolactone arm were taking 30 mg daily. Only 16% were still at the starting dose of 15 mg daily and a similar percentage of subjects in this arm was not taking study drug or had left the study.

Table 6. Daily Dose of Study Medication at Month 8

Daily Dose	SPIR N=1689 n (%)	Placebo N=1676 n (%)
0 mg [a]	271 (16.0)	221 (13.2)
15 mg	277 (16.4)	143 (8.5)
30 mg	889 (52.6)	983 (58.7)
45 mg	252 (14.9)	329 (19.6)

Source: Pitt et. al. online supplement (2), Table S2
Note: N for the trial arms does not include 33 and 47 subjects who died before Month 8 in the spironolactone and placebo arms, respectively.

a This row includes living, randomized subjects who had permanently stopped taking study drug prior to their Month 8 visit, regardless of whether they had continued in the study.

5.2 Efficacy Results

Efficacy for the overall study population will be described first, followed by the results in both of the study regions, the Americas and Eastern Europe. Risk information, which revealed no safety signals, will be presented for the overall population.

Overall Results

Efficacy results for the primary outcome, its components, and secondary outcomes are shown in **Table 7.** The unadjusted model was prespecified for the primary outcome analysis. Although the results numerically favored spironolactone over placebo, the results for the primary outcome were not statistically significant. The adjusted analyses were more favorable, but they also had 95% confidence intervals that did not exclude 1. However, results for both numerically important components of the primary endpoint, CV death and hospitalization for HF (HHF), favored spironolactone, and the CI for HHF did not cross 1 in the unadjusted analysis. The third component of the primary endpoint was aborted cardiac arrest, but there were very few of these in either arm. Results for stroke and MI were similar in the two arms.

Table 7. Results for the Primary Outcome, its Components and Secondary Outcomes
(All randomized subjects followed to study termination)

Outcome[1]	Number and % of Participants with Event (rate per 100 person-years)		*Unadjusted Model	Adjusted Model 1[2]	Adjusted Model 2[2]
	Spironolactone (N = 1722)	Placebo (N = 1723)	HR (S vs. P), 95% CI, *p*-value	HR (S vs. P), 95% CI, *p*-value	HR (S vs. P), 95% CI, *p*-value
Primary Outcome	**320 (18.6%) (5.9)**	**351 (20.4%) (6.6)**	**0.89 (0.77, 1.04) 0.138**	0.87 (0.75, 1.01) 0.071	0.87 (0.74, 1.01) 0.061
Primary Outcome Components					
CV Mortality	160 (9.3%) (2.8)	176 (10.2%) (3.1)	0.90 (0.73, 1.12) 0.355	0.89 (0.72, 1.10) 0.278	0.88 (0.71, 1.09) 0.253
Aborted Cardiac Arrest	3 (0.2%) (0.05)	5 (0.3%) (0.09)	0.60 (0.14, 2.50) 0.482	0.57 (0.14, 2.40) 0.439	0.58 (0.14, 2.44) 0.459
Hospitalization for Heart Failure	206 (12.0%) (3.8)	245 (14.2%) (4.6)	0.83 (0.69, 0.99) 0.042	0.80 (0.67, 0.96) 0.019	0.80 (0.66, 0.96) 0.017
Additional Secondary Outcomes					
All-Cause Mortality	252 (14.6%) (4.2)	274 (15.9%) (4.6)	0.91 (0.77, 1.08) 0.293	0.89 (0.75, 1.05) 0.163	0.88 (0.74, 1.05) 0.151
All-Cause Hospitalization	766 (44.5%) (18.8)	792 (46.0%) (20.0)	0.94 (0.85, 1.04) 0.248	0.93 (0.84, 1.03) 0.168	0.93 (0.84, 1.03) 0.161
Myocardial Infarction	65 (3.8%) (1.2)	64 (3.7%) (1.1)	1.00 (0.71, 1.42) 0.978	0.97 (0.69, 1.37) 0.868	0.98 (0.69 1.38) 0.899
Stroke	57 (3.3%) (1.0)	60 (3.5%) (1.1)	0.94 (0.65, 1.35) 0.733	0.93 (0.64, 1.33) 0.674	0.92 (0.64, 1.33) 0.669
Cumulative Heart Failure Hospitalization[3]	394 (6.8)	475 (8.3)	IRR (95% CI) = 0.75 (0.58, 0.97)		

Source: Pitt et. al. text and online supplement, Table S4 (2). Results for the primary outcome, its components and cumulative HHF were confirmed by the CDER statistical reviewer.
*Note: The study protocol specified use of the unadjusted model for the primary endpoint analysis.
1 Some participants experienced more than one component of the primary outcome, and are included once for the primary outcome, and once for each component they experienced.
2 This analysis includes pre---specified adjustments for age (as a continuous variable), diabetes history at baseline (insulin--treated, not insulin---treated, or no history of diabetes), and whether or not the participant had been hospitalized for heart failure as a major component in the six months prior to enrollment (adjusted model 1) or in the twelve months prior to enrollment (adjusted model 2).
3 All HF hospitalizations during the study were counted, with some patients contributing more than one event.

Figure 3 is a KM plot of the cumulative proportion of subjects who had a primary endpoint event from randomization to Month 72. The plot is consistent with the data in **Table 7**.

Figure 3. Cumulative Proportion of Subjects with the Primary Outcome to Month 72.

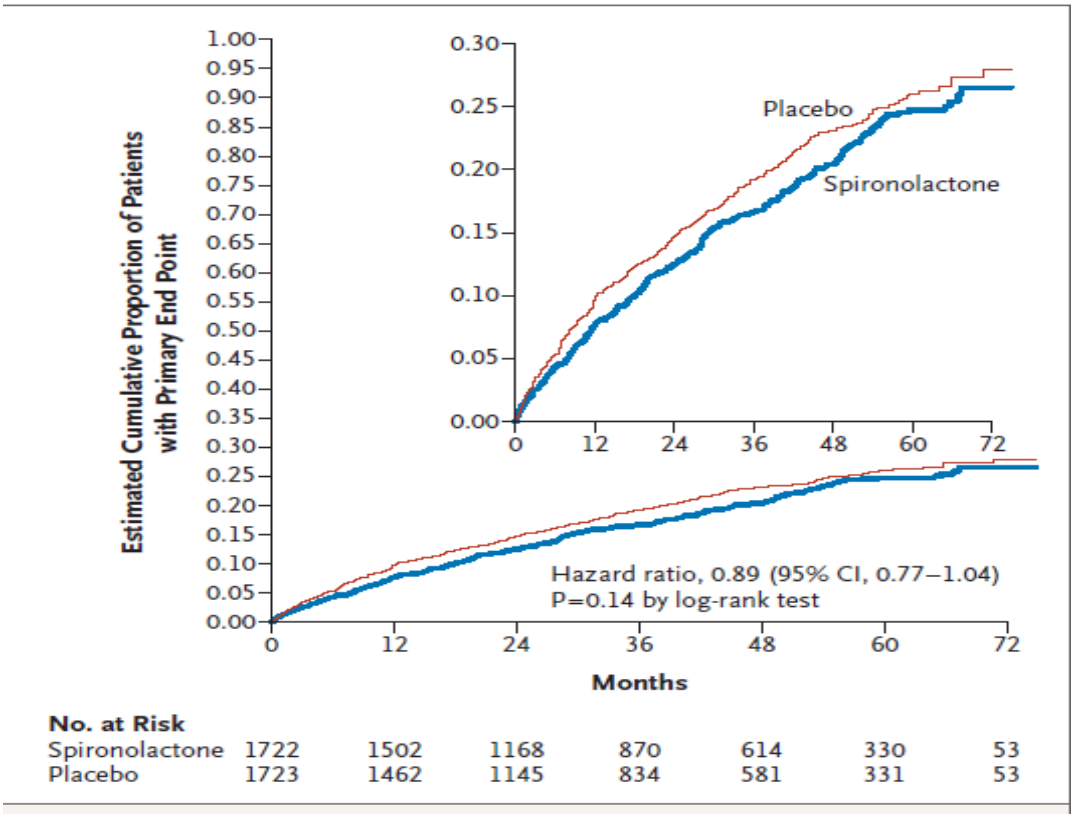


Figure 1. Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event.

The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. The inset shows the same data on an expanded y axis.

Source: Pitt et. al.(2), Figure 1

KCCQ Results

A TOPCAT publication by Lewis et.al. states, “The prespecified primary HRQL [health-related quality of life] outcome measure was the KCCQ overall summary score [OS]…”. (11) DCN has accepted the OS as a valid measure of QOL in patients with HF and have included results for this score in the labeling of tafamidis, which is approved to treat ATTR cardiomyopathy to reduce the rates of death and HHF.

The KCCQ OS was assessed in TOPCAT at baseline and Months 4, 12, and then yearly thereafter. Change scores from baseline were analyzed with an analysis of covariance using a backward selection model to select covariates that were significantly associated with change from baseline. Changes to all time points were assessed, with use of a Bonferroni correction to deal with multiplicity. Time was treated as a categorical variable and the interaction term of treatment and time was tested to examine whether the treatment group effect on change differed depending on the time point. The repeated-measures models were also repeated separately for subjects in both of the 2

regions (Americas and Eastern Europe), given the significant differences in patient characteristics and clinical outcomes.

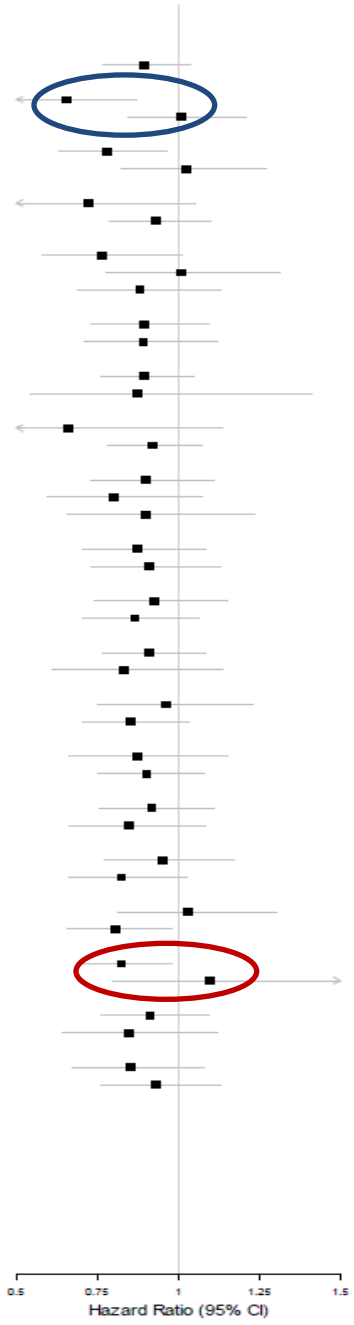
Compared to placebo, randomization to spironolactone was associated with a 1.36-unit (SE=0.44) greater change in the OSS (p=0.002) at Month 4. Region also affected change from baseline, with subjects in the Americas having a 2.1-unit larger increase in score at Month 4 than those in Eastern Europe, but none of these effects reflect clinically meaningful differences. Two other QOL scales did not show significant differences for the effects of spironolactone vs. placebo.

Efficacy Results in Subgroups

Figure 4 is a forest plot of the primary endpoint results in various subgroups of the randomized patient population. The plot provides the p-value for the interaction between each set of subgroups and the primary endpoint results.

Figure 4. Primary Outcome Results in Subgroups of All Randomized Patients

Subgroup	No. of Events/Patients	Hazard Ratio (95% CI)	P Value for Interaction
All Patients	671/3445 (19.5)	0.89 (0.77-1.04)	
Randomization Stratum			
Not hospitalized for heart failure in the year prior to study enrollment	194/981 (19.8)	0.65 (0.49-0.87)	0.01
Hospitalized for heart failure during that time period	477/2464 (19.4)	1.01 (0.84-1.21)	
Ejection fraction based on local reading			
Less than the median	347/1648 (21.1)	0.78 (0.63-0.96)	0.08
At or above the median	324/1796 (18.0)	1.02 (0.82-1.27)	
Ejection fraction based on local reading			
Less than 50%	112/520 (21.5)	0.72 (0.50-1.05)	0.22
Greater than or equal to 50%	559/2924 (19.1)	0.93 (0.79-1.10)	
Age			
50-64 years	201/1303 (15.4)	0.76 (0.58-1.01)	0.36
65-74 years	223/1194 (18.7)	1.01 (0.78-1.31)	
75 years or older	247/948 (26.1)	0.88 (0.69-1.13)	
Gender			
Male	374/1670 (22.4)	0.89 (0.73-1.09)	0.99
Female	297/1775 (16.7)	0.89 (0.71-1.12)	
Ethnicity			
Non-Hispanic	604/3124 (19.3)	0.89 (0.76-1.05)	0.94
Hispanic	67/321 (20.9)	0.87 (0.54-1.41)	
History of hypertension			
No	52/295 (17.6)	0.66 (0.38-1.14)	0.25
Yes	619/3147 (19.7)	0.92 (0.78-1.07)	
Diabetes mellitus			
No	344/2324 (14.8)	0.90 (0.73-1.11)	0.82
Yes, Insulin-treated	175/427 (41.0)	0.80 (0.59-1.07)	
Yes, Non-insulin-treated	152/691 (22.0)	0.90 (0.65-1.23)	
New York Heart Association congestive heart failure class			
II	323/2194 (14.7)	0.87 (0.70-1.08)	0.80
III & IV	321/1136 (28.3)	0.91 (0.73-1.13)	
Systolic blood pressure			
Less than the median	317/1419 (22.3)	0.92 (0.74-1.15)	0.67
At or above the median	354/2022 (17.5)	0.86 (0.70-1.06)	
Systolic blood pressure			
Less than 140 mm Hg	511/2569 (19.9)	0.91 (0.76-1.08)	0.62
Greater than or equal to 140 mm Hg	160/872 (18.3)	0.83 (0.61-1.14)	
Use of statins			
No	255/1637 (15.6)	0.96 (0.75-1.23)	0.46
Yes	416/1805 (23.0)	0.85 (0.70-1.03)	
Pulse pressure			
Less than the median	198/1117 (17.7)	0.87 (0.66-1.15)	0.85
At or above the median	473/2324 (20.4)	0.90 (0.75-1.08)	
Estimated GFR			
Less than the median	415/1722 (24.1)	0.92 (0.76-1.11)	0.62
At or above the median	256/1723 (14.9)	0.85 (0.66-1.08)	
Estimated GFR			
Less than 60 ml/min/1.73m2	351/1332 (26.4)	0.95 (0.77-1.17)	0.34
Greater than or equal to 60 ml/min/1.73m2	320/2113 (15.1)	0.82 (0.66-1.02)	
BMI			
Less than the median	278/1716 (16.2)	1.03 (0.81-1.30)	0.11
At or above the median	390/1719 (22.7)	0.80 (0.66-0.98)	
Geographic Region			
Americas	522/1767 (29.5)	0.82 (0.69-0.98)	0.12
Eastern Europe	149/1678 (8.9)	1.10 (0.79-1.51)	
Prior Myocardial Infarction			
No	476/2549 (18.7)	0.91 (0.76-1.09)	0.67
Yes	195/893 (21.8)	0.84 (0.64-1.12)	
Heart Rate			
Less than the median	271/1565 (17.3)	0.85 (0.67-1.08)	0.59
At or above the median	399/1875 (21.3)	0.93 (0.76-1.13)	
Racial category*			
White	539/3062 (17.6)		0.98
Black	104/302 (34.4)		
All Other	28/81 (34.6)		
Use of cardiac medication*			
No	2/16 (12.5)		0.94
Yes	669/3426 (19.5)		
Use of blood pressure lowering medication*			
No	2/26 (7.7)		0.94
Yes	669/3416 (19.6)		



* Due to imprecise estimates of the hazard ratio in groups with very few events, the hazard ratios, confidence intervals and linear plots are not included if one or more subgroup categories had fewer than 50 participants with a confirmed event.

Note: Results for subgroups based on geographic region are shown in the red ellipse; subgroups based on hospitalization in the year prior to enrollment are shown in the blue ellipse.
Source: Pitt et. al (2) Figure S3. Results for subgroups based on region and randomization stratum were confirmed by the CDER statistical reviewer. Some of these subgroup analyses were not prespecified.

The most extreme treatment-by-subgroup interaction involved subgroups based on enrollment (i.e., randomization) stratum (NP vs. HHF, interaction p=0.01, circled in blue). At p=0.12, the interaction by region is much less persuasive (circled in red).

Table 8 shows the results of the (unadjusted) primary endpoint analysis compared to two adjusted models, with the aim of detecting baseline variables affecting the outcome for the primary endpoint. Note that region has a powerful effect on outcomes in adjusted Model 2, the only model where it was included, and that as these variables are added to the model, the HR for spironolactone vs. placebo is reduced.

Table 8. Effects of Factors and Covariates on Primary Outcome Results

	Unadjusted Cox Model HR (95% CI) *p*-value	Adjusted Cox Model 1 HR (95% CI) *p*-value	Adjusted Cox Model 2 HR (95% CI) *p*-value
Spironolactone vs. Placebo	0.89 (0.77, 1.04) 0.138	0.87 (0.74, 1.01) 0.061	0.85 (0.73, 0.99) 0.043
Age (per year) at baseline		1.04 (1.03, 1.05) <0.001	1.02 (1.01, 1.03) <0.001
DM (insulin-treated) vs. no DM at baseline		3.99 (3.32, 4.79) <0.001	2.33 (1.91, 2.83) <0.001
DM (not insulin-treated) vs. no DM at baseline		1.67 (1.38, 2.02) <0.001	1.33 (1.09, 1.61) 0.004
Enrollment stratum (hospitalization vs. natriuretic peptide)		1.12 (0.94, 1.33) 0.214	1.65 (1.38, 1.98) <0.001
Region (Americas vs. Eastern Europe)			3.96 (3.22, 4.88) <0.001

1 Adjusted model 1 includes pre-specified adjustments for age (as a continuous variable), diabetes history at baseline (insulin---treated, not insulin-treated, or no history of diabetes), and whether or not the participant had been hospitalized in the twelve months prior to enrollment with management of heart failure as a major component.
2 Adjusted model 2 includes the pre-specified adjustments listed above in Footnote 1 and also geographic region.
Source: Pitt et. al. online supplement (2) Table S6 b

Table 9 shows the results for the primary endpoint by enrollment stratum. There is a strong interaction, with essentially neutral results in the prior HHF stratum and results strongly favoring spironolactone over placebo in the elevated NP stratum. For the primary endpoint, the event rate in the placebo arm of the NP stratum is numerically higher than the event rate in the placebo arm of the prior HHF stratum, suggesting that the populations are inherently different; however, the meaningfulness of this trend should not be overinterpreted.

Table 9. Primary Outcome Results by Enrollment Stratum

Outcome	P-value for interaction term	Prior HHF Stratum (N=2464)			NP Stratum (N=981)		
		Number and % with event (Rate per 100 person-years)		Unadjusted Model HR (95% CI), *p*-value	Number and % with event (Rate per 100 person-years)		Unadjusted Model HR (95% CI) *p*-value
		Spironolactone (N = 1232)	Placebo (N=1232)		Spironolactone (N = 490)	Placebo (N = 491)	
Primary Outcome	0.01	242 (19.6%) (6.0)	235 (19.1%) (6.0)	1.01 (0.84, 1.21) 0.923	78 (15.9%) (5.5)	116 (23.6%) (8.5)	0.65 (0.49, 0.87) 0.003
COMPONENTS of PRIMARY OUTCOME							
CV Mortality	0.11	120 (9.7%) (2.8)	117 (9.5%) (2.8)	1.01 (0.78, 1.31) 0.924	40 (8.2%) (2.7)	59 (12.0%) (3.9)	0.69 (0.46, 1.03) 0.069
Aborted Cardiac Arrest	--	1 (0.1%) (0.02)	5 (0.4%) (0.12)	0.20 (0.02, 1.69) 0.138	2 (0.4%) 0.13	0	--
HHF	0.09	151 (12.3%) (3.8)	162 (13.1%) (4.1)	0.92 (0.73, 1.14) 0.440	55 (11.2%) (3.9)	83 (16.9%) (6.1)	0.64 (0.46, 0.90) 0.011

Note: HHF=Hospitalization for Heart failure. Patients in the HHF stratum were enrolled based on hospitalization in the past year for which management of heart failure was a major component.

Note: NP=Natriuretic peptides. Patients in the NP stratum were enrolled based on meeting the NP entry criteria at baseline. Patient who met both entrance criteria are included in the prior hospitalization stratum.

Note: Patients may be represented in more than one row of the components

Source: Pitt et. al. (2) online supplement, Table S5 a (2). Results for the components of the primary endpoint were confirmed by the CDER statistical reviewer.

Table 10 shows results for the primary endpoint, its components, and cumulative HHF by region (the Americas vs. Eastern Europe). In the Americas, results for the primary endpoint favor spironolactone over placebo (10.4 vs. 12.6 events per 100 patient-years, p=0.026). Rates of CV death, first HHF, and cumulative HHF all favor spironolactone, and their 95% CIs for incidence rate ratios do not include 1.

In Eastern Europe, the rate of the primary endpoint was much lower than in the Americas and slightly favors placebo (2.5 vs. 2.3 events per 100 patient-years). The rate of cumulative HHF favors spironolactone, but the rate of these cumulative HHF events in each arm is less than 10% of the analogous rate in the Americas. The 95% CI of the IRR is wide, and the upper limit is 1.6.

Thus, the data from the Americas show a nominal 18% benefit for the primary endpoint with a point estimate of 2.2 fewer events per 100 patient-years. There were beneficial effects on the two major components of this endpoint, CV death and first HHF. There was also a 25% reduction in the rate of cumulative HHF with a point estimate of 5.1 fewer events per 100 patient-years. In Eastern Europe, event rates are markedly lower, and the primary endpoint analysis slightly favors placebo.

Table 10. Results by Region for the Primary Outcome, its Components and Cumulative Heart Failure Hospitalization

Region / Outcome	Spironolactone n (%)	Spironolactone n/100 pt-yr	Placebo n (%)	Placebo n/100 pt-yr	HR (95% CI) or *IRR (95% CI)
The Americas	**N=886**		**N=881**		
Primary Outcome	**242 (27.3)**	**10.4**	**280 (31.8)**	**12.6**	**0.82 (0.69, 0.98) *p*=0.026**
CV Death	96 (10.8)	3.6	127 (14.4)	4.9	0.74 (0.57, 0.97)
Aborted Cardiac Arrest	2 (0.2)	0.08	4 (0.5)	0.16	
HHF	184 (20.8)	7.9	216 (24.5)	9.7	0.82 (0.69, 0.99)
Cumulative HHF	**361**	**15.3**	**438**	**20.4**	**0.75 (0.58, 0.96)**
Eastern Europe	**N=836**		**N=842**		
Primary Outcome	**78 (9.3)**	**2.5**	**71 (8.4)**	**2.3**	**1.10 (0.79, 1.51)**
CV Death	64 (7.7)	2.0	49 (5.8)	1.6	1.31 (0.91, 1.90)
Aborted Cardiac Arrest	1 (0.1)	0.03	1 (0.1)	0.03	
HHF	22 (2.6)	0.72	29 (3.4)	0.95	0.76 (0.44, 1.32)
Cumulative HHF	**33**	**1.1**	**37**	**1.4**	**0.83 (0.42, 1.62)**

HHF=Hospitalization for heart failure; IRR=incidence rate ratio
N and the rate of cumulative HHF events are based on the total n of events in each treatment arm, not the n of patients with events. pt-yr=patient-year

Source: Pfeffer et. al. (3)
*Statistical methods are reported to be the same as for the overall analysis, meaning that the p value for the primary endpoint was calculated using a log-rank test and the cumulative HHF analyzed using a negative binomial model.

Rates of HHF excluding the first were 7.4 vs. 10.7 events per 100 patient-years for spironolactone and placebo, respectively (IRR=0.69) in the Americas and 0.38 vs. 0.45 events per 100 patient years (IRR=0.84) in Eastern Europe.

A further analysis of the results for cumulative HHF, the study outcome with the greatest number of events, was performed to examine the interaction between region and enrollment stratum by the statistical reviewer, Dr. Ququan Liu of CDER's Office of Biostatistics. (**Table 11**). In the top half of the table, enrollment stratum was determined using the 2-category methodology used in the study publications: the previous HHF stratum ("Pre-HHF") included all subjects who qualified with a previous HHF in the 12 months prior to enrollment, regardless of whether they did or did not have elevated natriuretic peptides at baseline. The "No-pre-HHF" stratum included those who qualified with elevated natriuretic peptides at baseline and had no HHF in the previous 12 months. The bottom half of the table differs in that there are 3 categories of qualification: having only an HHF in the 12 months prior to enrollment, only elevated natriuretic peptides at baseline, and both.

Table 11. Results for the Interaction Between Region and Enrollment Stratum for Endpoint of Cumulative Heart Failure Hospitalization

		Number of Events (Incidence Rate per 100 patient-yrs)		
		Spironolactone (N=1722)	Placebo (N=1723)	IRR (95% CI)
Overall (N=3445) – Two categories of enrollment strata				
Randomization Stratum	Pre-HHF (n=2464)	303 (7.1)	309 (7.3)	0.85 (0.62, 1.15)
	No pre-HHF, ↑NP (n=981)	91 (6.1)	166 (11.1)	0.56 (0.34, 0.90)
Americas (n=1767)				
Randomization Stratum	Pre-HHF (n=976)	270 (18.8)	272 (20.5)	0.81 (0.58, 1.11)
	No preHHF, ↑ NP (n=791)	91 (7.6)	166 (13.3)	0.58 (0.39, 0.86)
Eastern Europe (n=1678)				
Randomization Stratum	Pre-HHF (n=1488)	33 (1.2)	37 (1.3)	0.84 (0.43, 1.66)
	No pre-HHF, ↑NP (n=190)	0	0	-
Overall (N=3445) -- Three categories of enrollment strata				
Randomization Stratum	Pre-HHF, no ↑NP (n=1909)	139 (4.0)	176 (5.0)	0.70 (0.49, 0.99)
	Both pre-HHF & ↑NP (n=555)	164 (20.1)	133 (18.8)	0.97 (0.57, 1.68)
	No pre-HHF, ↑NP (n=981)	91 (6.1)	166 (11.1)	0.56 (0.36, 0.87)
Americas (n=1767)				
Randomization Stratum	Pre-HHF, no ↑NP (n=606)	109 (12.4)	143 (15.7)	0.68 (0.45, 1.04)
	Both pre-HHF & NP (n=370)	161 (28.6)	129 (30.9)	0.86 (0.52, 1.40)
	No pre-HHF, ↑NP (n=791)	91 (7.6)	166 (13.3)	0.58 (0.39, 0.85)
Eastern Europe (n=1678)				
Randomization Stratum	Pre-HHF, no ↑NP (n=1303)	30 (1.2)	33 (1.3)	0.82 (0.39, 1.67)
	Both pre-HHF & ↑NP (n=185)	3 (1.2)	4 (1.4)	1.12 (0.14, 8.94)
	No pre-HHF, ↑NP (n=190)	0	0	-

Source: Analysis by the FDA Statistical Reviewer, using a negative binomial model.

For the 3-category analysis, results in the Americas, like the overall results, suggest that subjects who qualified on the basis of having both a previous HHF in the 12 months prior to randomization and an elevated natriuretic peptide level at baseline had by the far the highest rates of recurrent HHF during the trial, regardless of treatment arm. Results in each stratum favored spironolactone over placebo in the Americas. There were strikingly few events in patients from Eastern Europe.

Evidence for Regional Differences in the Patients Enrolled

To examine possible explanations for the observed differential effects of spironolactone in the two study regions, the TOPCAT investigators analyzed demographic and disease-related factors in the regions. Characteristics of enrolled patients in the Americas and Eastern Europe are shown in **Table 12**. Compared to patients in the Americas, patients in Eastern Europe were considerably younger, were more likely to be white, and tended to have less severe (Class I or Class II) HF. They were far more likely to have been admitted to the study on the basis of a prior HHF than by an elevated NP level than patients in the Americas. They had a higher median diastolic BP, and a lower median BMI. Also, they had a higher median eGFR and a higher median hemoglobin. They had a much higher rates of "CV disease history,"[4] angina, and aspirin use, and higher rate of prior MI. They had lower rates of diabetes, chronic renal disease, and atrial fibrillation. In short, the patients from Eastern Europe were a younger population with more evidence of ischemic heart disease. They seemed less like the typical subject with HFpEF, who are often obese, diabetic and have an increased rate of atrial fibrillation.

Table 12. TOPCAT -- Regional Subject Characteristics at Baseline*

Characteristic	Americas (N = 1767)	Eastern Europe (N = 1678)
Age — yrs.	72 (64, 79)	66 (59, 71)
Age ≥75 yd — n (%)	720 (41)	228 (14)
Female sex — n (%)	882 (50)	893 (53)
White race — n (%)	1384 (78)	1678 (100)
LVEF - %	58 (53, 64)	55 (50, 60)
NYHA class — n (%)		
I	99 (6)	10 (1)
II	1043 (59)	1151 (69)
III	610 (35)	511 (30)
IV	10 (1)	5 (<1)
Eligibility Stratum – n (%)		
Elevated NPs	791 (45)	190 (11)
HF Hospitalization	976 (55)	1488 (89)
Current Smoker	117 (7)	243 (14)
Heart Rate (BPM)	68 (61, 76)	68 (62, 75)
BP – mmHg		
Systolic	129 (118, 138)	130 (120, 140)
Diastolic	70 (62, 80)	80 (80, 85)
BMI	32.9 (28.0, 38.4)	29.4 (26.7, 33.2)
Serum K – mEq/L	4.2 (3.9, 4.5)	4.4 (4.1, 4.7)
Serum Cr – mg/dL	1.1 (0.9, 1.4)	1.0 (0.9, 1.1)

[4] This term is not defined in the study publications.

Characteristic	Americas (N = 1767)	Eastern Europe (N = 1678)
eGFR – mL/min/1.73 m^2	61 (49, 77)	69 (58, 81)
Hemoglobin – g/dL	12.8 (11.7, 14.0)	13.7 (12.6, 14.8)
CV disease history, n (%)	815 (46)	1208 (72)
Atrial fibrillation, n (%)	743 (42)	471 (28)
Diabetes mellitus, n (%)	788 (45)	330 (20)
Chronic kidney disease, n (%)	855 (48)	477 (28)
Myocardial infarction, n (%)	359 (20)	534 (32)
PCI or CABG, n (%)	567 (32)	246 (15)
Angina, n (%)	486 (28)	1127 (67)
Stroke, n (%)	158 (9)	107 (6)
Medications, n (%)		
Diuretic	1573 (89)	1244 (74)
ACEI or ARB	1395 (79)	1505 (90)
β-Blocker	1387 (79)	1289 (77)
Calcium channel blocker	682 (39)	612 (36)
Aspirin	1027 (58)	1223 (73)
Statin	1148 (65)	657 (39)
Long-acting nitrate	305 (17)	209 (12)
Warfarin	592 (34)	195 (12)

*Note: All continuous variables are presented as the median (intra-quartile range)
Source: Pfeffer et. al., Table 1 (3)

Of note, the rates of the primary outcome, CV death and HHF in the placebo arm in Eastern Europe are substantially lower than in the corresponding results in the Americas, suggesting that the patients in Eastern Europe had a considerably lower risk at baseline for primary endpoint events (**Table 10**). Combined with the differences in the baseline characteristics of patients in the two regions and the low rate of study qualification on the basis of NPs in Eastern Europe, one can infer, at a minimum, that patients in Eastern Europe differed substantially from those in the Americas. Those in Eastern Europe were younger, had fewer risk factors for HFpEF, and were plainly at much lower risk of CV death and HF hospitalization. The had more characteristics suggesting ischemic heart disease, which may have been the cause of their qualifying hospitalization, rather than heart failure. It seems possible that a substantial fraction of them did not have heart failure.

Table 13 shows NYHA distribution data and results for CV death and HHF in the placebo arms of 3 other HFpEF trials [I-Preserve(7), CHARM-Preserved(8), and PEP-CHF(6)], as well the analogous regional data from TOPCAT. Rates of CV death and HHF are substantially lower in Eastern Europe than in any of the other three studies or the TOPCAT results in the Americas. Note that event rates were not reported in a similar fashion across the studies, but this does not affect the conclusion that event rates in Eastern Europe in TOPCAT were lower than other rates displayed in the table.

Table 13. Placebo Arm Data from Published HFpEF Trials vs. TOPCAT

Study	I-Preserve	CHARM-Preserved	PEP-CHF	TOPCAT Americas	TOPCAT E. Europe
N	2061	1509	426	881	842
NYHA Class	II-IV	II-IV	I-IV	II-IV	II-IV
% Class II/III	22/76	60/39	74/26 [f]	60/34	69/30
EVENT RATES [a]					
CV Death	3.6	11.3% [c]	9.4% [g]	4.9	1.6
HHF	4.4	18.3% [c]	~ 18% [g]	9.7	0.95
Composite [b]	5.7 [d]	9.1	13.2 [h]	12.6 [e]	2.3 [e]

[a] First events per 100 patient-years unless otherwise specified
[b] Composite of CV death and HHF unless otherwise specified
[c] Percent with events over a median study period of 36.6 months
[d] Rate for composite of death from any cause and CV hospitalization
[e] Composite rate includes a small contribution (<0.2/100 patient-years) of patients with an aborted cardiac arrest
[f] Class I and II/Class III and IV
[g] Percent with events over a mean follow-up of 26 months
[h] Composite of all-cause death and HHF.

Thus, rates of death and HHF in the placebo arms of earlier placebo-controlled trials of drugs for HFrEF were more in-line with the results of TOPCAT from the Americas, and consistently higher than those in the TOPCAT results in Eastern Europe. These data strongly suggest that there were major differences between patients enrolled in the two TOPCAT regions, and also suggest that a substantial fraction of those enrolled in Eastern Europe may not have had heart failure.

Differences between the TOPCAT regions in terms of enrollment stratum and the rate of the primary study outcome were noticed during the trial by the study DMC, which was chaired by Dr. Michael Bristow. In addition, there were concerns over extremely rapid enrollment in Eastern Europe, especially in Georgia. Accordingly, the trial leadership instituted a "BNP pilot program" in Russia and Georgia "…to allow comparison of the patients randomized through the hospitalization or biomarker pathways." The same publication also noted that "an NHLBI Program staff member fluent in Russian" had reviewed 22 index hospitalization discharge summaries from enrolled subjects in Russia and found that "very few patients" [only 2 or possibly 3 out of 22 total records reviewed] "had presentations consistent with heart failure." The publication went on to state that "The DSMB Chair reviewed the same (Russian translated) material and concluded "the presenting complaints, admission and discharge diagnoses indicated that the majority of patients were likely suffering from acute ischemic symptoms, not HF per se. Specifically, in the majority of patients there is no documentation that heart failure was a major component of the index hospitalization."

Results of the BNP pilot program, which also included data from the US and Canada, are shown in **Table 14**. The highlighted data indicate that for subjects who were enrolled based on a prior hospitalization for HF and who also had BNP or NT-proBNP data, the percentage of such patients with elevated levels of NPs was 46% in Russia, 36% in Georgia, and 91% in the US and Canada. However, it is noted in the publication that patients in this analysis from the Americas had their NP levels tested during their hospitalization, while those in Eastern Europe had their levels drawn "where the test was available," suggesting that they might have been tested after discharge from the

hospital. In one publication of a longitudinal study unrelated to TOPCAT, NT-proBNP levels fell 37% between admission and discharge in patients with acute decompensated HF who were discharged alive, but there were no data for those with HFpEF vs HFrEF.(13) Thus, the comparison of NP levels in the two regions may be confounded. Nonetheless, as noted above, the regional differences in the rates of CV death and HHF strongly suggest that there were important differences between the patients who were enrolled in the Americas and those from Eastern Europe.(14)

Table 14. Results of the Natriuretic Peptide Pilot Project, BNP or NT-proBNP

***Country/Region*, Group**	**# of**	**BNP ≥100 or NT-proBNP ≥360**			**Median,**	**Range,**
U.S. and Canada	**Subjects**	**Yes**	**No**	**% Yes**	**pg/ml**	**pg/ml**
Eligible via Hosp (BNP)	137	124	13	91	332	4-2382
Eligible via Hosp (NT-proBNP)	42	39	3	93	887	43-7903
Eligible via Hosp, either NP	179	163	16	91*	–	–
Eligible via BNP	245	245	0	100	223	100-2686
Eligible via NT-proBNP	103	103	0	100	901	360-3814
Total # of Subjects	527	–	–	–	–	–
Russia						
Eligible via Hosp (BNP)	22	15	7	68	168	8-2399
Eligible via Hosp (NT-proBNP)	94	38	56	40	233	13-3294
Eligible via Hosp, either NP	116	53	63	46*	–	–
Eligible via BNP	8	8	0	100	178	113-119
Eligible via NT-proBNP	38	38	0	100	920	382-3406
Total # of Subjects	162				–	–
Georgia						
Eligible via Hosp (BNP)	2	2	0	100	1015	958-1072
Eligible via Hosp (NT-proBNP)	12	3	9	25	164	20-1800
Eligible via Hosp, either NP	14	5	9	36*	–	–
Eligible via BNP	8	8	0	100	450	129-913
Eligible via NT-proBNP	45	45	0	100	1572	393-15394
Total # of Subjects	67	–	–	–	–	–
Russia and Georgia Combined						
Eligible via Hosp (BNP)	24	17	7	71	217	8-2399
Eligible via Hosp (NT-proBNP)	106	41	65	39	208	13-3294
Eligible via Hosp, either NP	130	58	72	45*	–	–
Eligible via BNP	16	16	0	100	211	113-913
Eligible via NT-proBNP	83	83	0	100	1175	382-15394
Total # of Subjects	229	–	–	–	–	–

Hosp = heart failure hospitalization entry criterion; *p <0.001 (Bonferroni critical value = 0.0167) vs. U.S./Canada, Eligible via Hosp, either NP
Source: TOPCAT DMC publication supplement, Table 1 (14). Data for South America were not provided.

Evidence for Regional Differences in Compliance with Study Medication

Because spironolactone is an antagonist of endogenous aldosterone, patients who take this drug characteristically have dose-dependent decreases in blood pressure as well as dose-dependent increases in serum potassium and creatinine. All of these changes are related to reduced aldosterone agonism, are evident within several weeks of starting treatment, and are generally maintained during treatment with spironolactone.

Table 15 shows categorical results for changes in serum creatinine and potassium during treatment in the two treatment arms in the Americas and in Eastern Europe. Of note, the nominal mean daily dose of study drug in spironolactone arm patients at Month 4 (the visit of the optional, final up-titration to 45 mg), was higher in Eastern Europe than in the Americas (30 mg vs 24 mg), despite the evidence of underdosing in the former region compared to the latter based on PD markers and canrenone levels. Directionally similar findings were observed at Month 12 (28 mg vs. 19 mg) and Month 18 (25 mg vs. 16 mg).(3) Consistent with the data shown in **Figure 5**, the specified categorical changes involving elevations of serum potassium and serum creatinine were substantially more frequent in spironolactone arm patients in the Americas than in Eastern Europe. Also, data from the spironolactone arm differed markedly from the placebo arm in the Americas, but the differences between the study arms were substantially less in Eastern Europe. As expected with a drug that tends to increase levels of serum potassium, hypokalemia occurred at a substantially lower rate in the Americas in the spironolactone arm than in the placebo arm. The difference between the two treatment arms in the rate of hypokalemia was small in Eastern Europe.

Table 15 also includes data from a post-study examination of frozen repository serum samples obtained from subjects at selected sites TOPCAT. During study treatment, sera were saved in a repository from patients in the spironolactone arm who *reported compliance with study medication* at the time of phlebotomy. These samples were assessed for the presence of canrenone, a metabolite of spironolactone with a long half-life. Serum canrenone levels were below the lower limit of detection in 20 of 66 subjects (30%) from Eastern Europe, compared to 2 of 76 subjects (3%) from the Americas.(15) These data suggest a high rate of non-compliance in patients with self-reported high compliance in Eastern Europe, but not in the Americas. The lack of compliance with study medication indicated by these data could explain the reduced magnitude of the expected PD effects of spironolactone in Eastern Europe.

Figure 5 includes plots over the course of TOPCAT for these 3 parameters in the Americas and Eastern Europe (labeled Russia/Georgia) in the two treatment arms. Although there are differences between regions for each parameter at baseline, probably due to differences in age, intensity of medical treatment and perhaps disease-related factors, the baseline values are similar within each region in the two treatment arms. During treatment with spironolactone, the expected changes in the 3 aldosterone-related PD parameters are observed. However, between-arm differences during treatment are much larger in the Americas than in Eastern Europe for each parameter, suggesting that compliance with spironolactone therapy may have been substantially less in Eastern Europe than in the Americas. The treatment by region interaction term had a *p*-value <0.001 for each PD parameter.

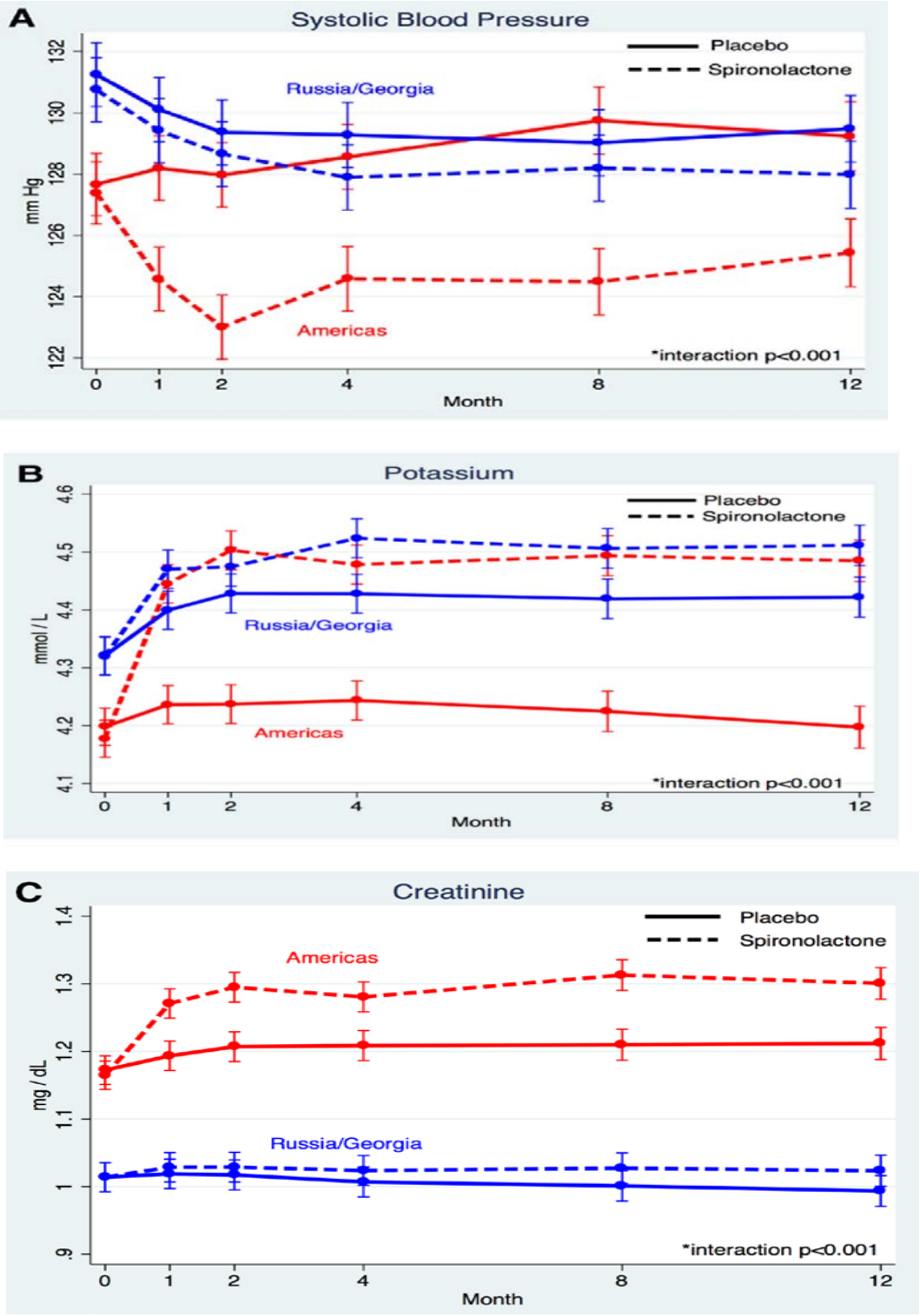
In summary, the canrenone level data from the repository study and the data regarding the pharmacodynamic effects of spironolactone are consistent in suggesting that non-compliance with study medication may have been substantially more frequent in Eastern Europe than in the Americas.

Table 15. Regional Results for Assessments Related to Spironolactone PD & PK

Region / Outcome	Spironolactone n (%)	Spironolactone %/year	Placebo n (%)	Placebo %/year	HR or **OR (95% CI)
The Americas	**N=886**		**N=881**		
Doubling of baseline serum creatinine	158 (17.8)	6.8	102 (11.6)	4.2	1.60 (1.25-2.05)
Creatinine ≥ 3.0 mg/dL	87 (9.8)	3.5	80 (9.1)	3.2	1.10 (0.81-1.49)
Potassium ≥ 5.5 mEq/L	223 (25.2)		78 (8.9)		**3.46 (2.62-4.56)
Potassium < 3.5 mEq/L	135 (15.2)		231 (26.2)		**0.51 (0.40-0.64)
Canrenone < LLD	2/76 (3)				
Eastern Europe	**N=836**		**N=842**		
Doubling of baseline serum Cr	17 (2.0)	0.6	18 (2.1)	0.6	0.95 (0.49-1.85)
Creatinine ≥ 3.0 mg/dL	2 (0.2)	0.1	4 (0.4)	0.2	0.50 (0.09-2.75)
Potassium ≥ 5.5 mEq/L	99 (11.8)		79 (9.4)		**1.30 (0.95-1.77)
Potassium < 3.5 mEq/L	144 (17.2)		163 (19.4)		**0.87 (0.68-1.11)
Canrenone < LLD	20/66 (30)				

Note: All samples from serum. Analyses of potassium and creatinine count a patient's post-baseline assessment that met the described criterion at any time. IRR=Incidence rate ratio; OR=Odds ratio; LLD=Lower limit of detection
** Denotes odds ratio, otherwise, the statistic is the hazard ratio
Note: The analysis of canrenone includes only subjects assigned to spironolactone who reported taking study drug
Sources: adapted from Pfeffer et. al.(3); DeDenus et. al.(15)

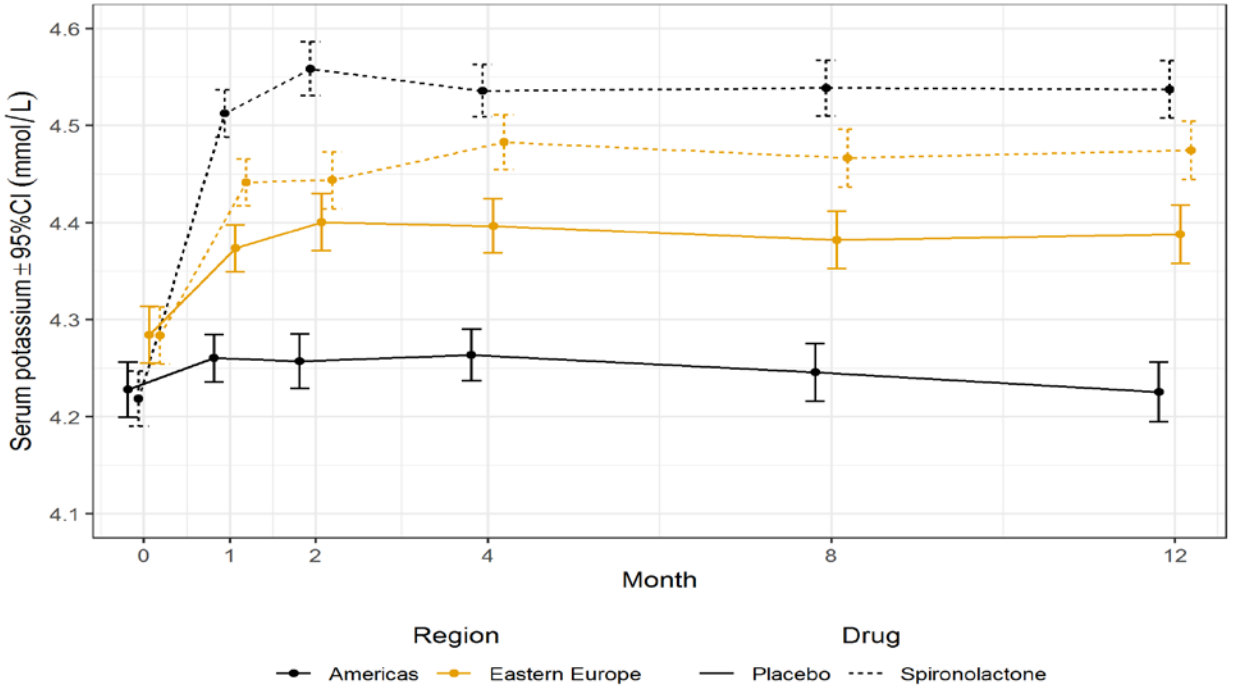
Figure 5. Serial Values for Spironolactone PD Markers by Region and Treatment Arm



Source: Pfeffer et. al. (3)

Using the study database, Dr. Lars Johannesen of DCN confirmed the above information on systolic blood pressure and creatinine. For serum potassium, however, he found differences between the Americas and Eastern Europe that are more extreme than the ones in the publication by Pfeffer et. al. (**Figure 6**).

Figure 6. Serial Values for Serum Potassium by Region and Treatment Arm (FDA Analysis)



Source: Analysis by Dr. Lars Johannesen, DCN

Additional analyses by statistical reviewer

There are considerable differences in enrollment stratum and the rate of the primary study outcome between Eastern Europe and Americas. Questions were raised as to whether Eastern European patients qualified by prior history of HHF were, in fact, typical for a HFpEF population. However, the statistical reviewer noted that the lack of treatment effect in patients qualified with a previous HHF existed not only in Eastern Europe, where the majority of patients qualified with a previous HHF, but also in the Americas (Table 16). Although two regions showed quite some differences in patient populations, patients qualified by a previous HHF in both regions appeared to show no treatment effect. This seems to contradict the hypothesis that different populations between two regions led to different outcome. For patients in the Americas, event rates tended to be much higher in those enrolled with a prior HHF than those enrolled with an elevated BNP; however, the treatment effect was less. Though one might wish to speculate about possible explanations for these subgroup findings, the data are difficult to interpret and would be easy to overinterpret.

Table 16. Primary Outcome Results by Region and Enrollment Stratum

	No. of Event (%) [Incidence Rate per 100 patient-year]					
	Previous HHF			Elevated BNP		
Overall	Spironolactone (N=1232)	Placebo (N=1232)	HR (95% CI)	Spironolactone (N=490)	Placebo (N=491)	HR (95% CI)
	242 (19.6) [6.1]	235 (19.1) [6.0]	1.01 (0.84 1.21)	78 (15.9) [5.5]	116 (23.6) [8.5]	0.65 (0.49 0.87)
Americas	Spironolactone (N=500)	Placebo (N=476)		Spironolactone (N=386)	Placebo (N=405)	
	172 (34.4) [14.1]	169 (35.5) [15.4]	0.92 (0.75 1.14)	70 (18.1) [6.3]	111 (27.4) [9.9]	0.63 (0.47 0.85)
Eastern Europe	Spironolactone (N=732)	Placebo (N=756)		Spironolactone (N=104)	Placebo (N=86)	
	70 (9.6) [2.5]	66 (8.7) [2.3]	1.08 (0.77 1.51)	8 (7.7) [2.7]	5 (5.8) [2.0]	1.35 (0.44 4.13)

In TOPCAT, the Americas included 4 countries from 2 continents (Table 17). The incidence rate for the primary endpoint and cumulative HHF differ considerably among continents. The rates were highest in North America, intermediate in South America, and lowest in Eastern Europe (Table 18). Thus, patients in the Americas are heterogeneous.

Table 17. Subjects Randomized by Country

Country	Spironolactone (N=1722) no. (%)	Placebo (N=1723) no. (%)
US	572 (33.2)	579 (33.6)
Canada	166 (9.6)	160 (9.3)
Brazil	85 (4.9)	82 (4.8)
Argentina	63 (3.7)	60 (3.5)
Russia	529 (30.7)	537 (31.2)
Republic of Georgia	307 (17.8)	305 (17.7)

Table 18. Rate of Primary Endpoint and Cumulative HHF by Continent

	No. of Event (%) [Incidence Rate per 100 patient-yr]					
	Spironolactone			Placebo		
	N	Primary endpoint	Cumulative HHF	N	Primary endpoint	Cumulative HHF
Overall	1722	320 (18.6) [5.9]	394 (22.9) [6.8]	1723	351 (20.4) [6.6]	475 (27.6) [8.3]

North America	738	214 (29.0) [10.8]	324 (46.4) [15.1]	739	246 (33.3) [12.9]	409 (55.3) [18.2]
South America	148	28 (18.9) [7.9]	19 (12.8) [5.1]	142	34 (23.9) [11.2]	29 (20.4) [8.9]
Eastern Europe	836	78 (9.3) [2.5]	33 (3.9) [1.1]	842	71 (8.4) [2.3]	37 (4.4) [1.2]

5.3 Safety Results

Data for deaths in TOPCAT are shown in **Table 19**. As expected from the efficacy results, there were fewer CV deaths with spironolactone. There is modest imbalance in GI-related deaths favoring spironolactone, but the rate of GI SAEs was similar in the two arms (**Table 20**). There was an imbalance of deaths of unknown cause favoring spironolactone. No actionable signals of harm are apparent.

Table 19. Adjudicated Deaths from Randomization to End of Follow-up

	SPIRONOLACTONE N=1722		PLACEBO N=1723	
	N	%	N	%
CV death	**160**	**9.3%**	**176**	**10.2%**
· MI	16	0.9%	17	1.0%
· Pump Failure	28	1.6%	39	2.3%
· Sudden Death	56	3.3%	55	3.2%
· Presumed Sudden Death	7	0.4%	10	0.6%
· Presumed CV death	33	1.9%	33	1.9%
· Stroke	15	0.9%	10	0.6%
· Embolism	1	0.1%	1	0.1%
· CV procedure	1	0.1%	5	0.3%
· Other	3	0.2%	6	0.3%
Non--CV death	**74**	**4.3%**	**71**	**4.1%**
· Infection	21	1.2%	16	0.9%
· Malignancy	27	1.6%	25	1.5%
· Pulmonary	9	0.5%	5	0.3%
· GI	4	0.2%	13	0.8%
· Renal	2	0.1%	0	0.0%
· Hyperkalemia	0	0.0%	0	0.0%
· Accidental	4	0.2%	4	0.2%
· Suicide	0	0.0%	0	0.0%
· Diabetes	1	0.1%	0	0.0%
· Other	6	0.3%	8	0.5%
Unknown Cause	**18**	**1.0%**	**27**	**1.6%**

Source: Pitt et. al. online supplement (2), Table S7

Data for SAEs in TOPCAT are shown in **Table 20**. The rate of serious AEs was 41.6 vs. 41.8 events per 100 patient-years in the spironolactone and placebo arms, respectively. The protocol and publications are not clear regarding the timing of SAEs that are included in this analysis. No new signals of harm are apparent.

Table 20. SAEs in TOPCAT

	SPIRONOLACTONE N=1722		PLACEBO N=1723	
CATEGORY	**N**	**%**	**N**	**%**
Any Serious Adverse Event	835	48.5	855	49.6
Auditory/Ocular	13	0.8	11	0.6
Cancer	53	3.1	50	2.9
Cardiovascular	578	33.6	566	32.8
Endocrine and Metabolic	62	3.6	45	2.6
Gastrointestinal	107	6.2	105	6.1
Hematological	29	1.7	31	1.8
Hepatobiliary/Pancreas	22	1.3	25	1.5
Infection	64	3.7	73	4.2
Musculoskeletal/Skin	111	6.4	104	6.0
Neurological/Psychiatric	96	5.6	102	5.9
Pulmonary/Upper Respiratory	144	8.4	156	9.1
Renal/Genitourinary	116	6.7	89	5.2
Sexual/Reproductive Function	6	0.3	7	0.4

Source: Pitt et. al. online supplement (2), Table S8 (2)
Note: AE category was assigned by the investigator.

Also, Information on non-serious SAEs was provided in a table in the report of the study that was submitted by NIH to the TOPCAT IND 71883. However, the table provides a count of the total N of AEs that occurred after randomization by study arm, not the number of patients with individual AEs. The submission does not state how these AEs are related to the timing of study drug, their level of severity, their assessed relatedness to study drug or what dictionary used to classify the events. The data are thus difficult to interpret.

Of note, it is common for DCN to allow sponsors of drugs to reduce collection and reporting of non-serious AEs from studies intended to establish a new indication for a marketed product if the AE profile of the drug is well-established. TOPCAT is such a study, and the new indication is closely related to the currently approved HFrEF indication for spironolactone. Safety information from the large, placebo-controlled RALES study in patients with HFrEF is already in labeling. In addition, we have interpretable data from TOPCAT for deaths, SAEs, adverse dropouts and the clinical consequences of the PD effects of spironolactone.

Conclusions regarding safety

The reported safety data are consistent with labeling and disclose no new safety signals for spironolactone.

6. Advisory Committee Meeting

An advisory committee meeting is warranted because of the controversial nature of using post-hoc analyses to support addition of a new indication for a marketed product. If approved, spironolactone may be first product with an indication to improve outcomes in patients with HFpEF. We should obtain input from our AC. A meeting has been tentatively scheduled for Dec. 16, 2020.

7. Labeling

No one has submitted labeling for a HFpEF indication for spironolactone. One possibility is modifying the current HF indication in Sec. 1 to create a unitary indication inclusive of adult patients regardless of ejection fraction:

> "Spironolactone (tablets or suspension) are/is indicated for the treatment of adults with heart failure to reduce the rates of cardiovascular death and hospitalization for heart failure."

However, subjects with EF in the range of 36% to 44% were excluded from both RALES and TOPCAT. It might be useful to perform analyses of the efficacy of spironolactone in the subjects with EF in the lowest quintile of EF (or some other fraction) in TOPCAT and the highest quintile in RALES to get some feel for efficacy in patients with EF approaching the excluded range. These data might inform labeling .

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